Cytological Features of Malignant Metastatic Ameloblastoma: A Case Report and Differential Diagnosis

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In this report, the cytological features and differential diagnosis of the metastasis from and subsequent local recurrence of an unusual case of malignant (metastatic) ameloblastoma are described, with histological confirmation. Characteristic cytological findings included fibrovascular central cores surrounded by palisading crowded basaloid or columnar cells or both and rosette-like structures of tumor cells with central fibrillary material. Keratin debris in the background and cystic cavities were prominent components of the metastatic ameloblastoma. The basaloid cells showed scant-to-absent cytoplasm, round-to-oval to tear-shaped nuclei, rare longitudinal nuclear grooves, single or multiple nucleoli, and smooth-to-clefted nuclear contours. No features to predict malignant behavior were identified (abundant mitotic activity, necrosis, nuclear pleomorphism). The cytological features of ameloblastoma appear to be characteristic enough to allow definitive diagnosis. However, since the cytology of this tumor is underreported in the literature, the unwary observer could easily misdiagnose it, especially at metastatic sites

Key Words: malignant ameloblastoma; metastatic ameloblastoma; needle aspiration

Ameloblastoma is a rare epithelial odontogenic tumor, which makes up about 1% of tumors and cysts originating in the jaws.1 Although ameloblastoma has bland cytology and slow growth, it can be locally aggressive and recur multiple times, meriting a long follow-up period.2-4 The metastatic (malignant) ameloblastoma is even rarer, with fewer than 50 cases describing its histology in the English literature.2-7 It resembles ameloblastoma histologically and is distinguished from ameloblastoma by the demonstration of metastases.2,3

The cytological findings of ameloblastoma on fine-needle aspiration biopsy (FNAB) specimens have been underreported in the literature.8-13 We report the fine-needle aspiration biopsy (FNAB) findings of both the metastasis and subsequent local recurrence of a malignant (metastatic) ameloblastoma, with histological confirmation. This case has unusual features, in that the lung metastasis was identified 35 years after excision of the primary ameloblastoma, and there was not a characteristic history of frequent surgical procedures or multiple local recurrences prior to the development of metastatic disease.

Case Report

A 53-year-old woman presented with a new painless 5-cm right mandibular mass, which bulged from the intraoral lingual mucosal surface. Her past medical history was significant for excision of a right mandibular ameloblastoma at the same site, 45 years previously (age 8), at another institution. Subsequently, 35 years later (age 43), a recurrent invasive ameloblastoma was resected en bloc from the same right mandibular site. As well, metastatic ameloblastoma was identified in the left lower lobe of the lung by FNAB, and a lobectomy was performed. Metastatic ameloblastoma was again resected from the lung (right middle lobe), 2 years later (age 45).

FNAB of the most recent mass was performed by two cytopathologists with a 23-gauge needle using an intraoral approach with multiple passes. FNAB of the left lung nodule was performed by an interventional radiologist using radiological guidance. The material was prepared on non-frosted slides and fixed in 95% alcohol or air-dried. The wet fixed samples were stained either with hematoxylin and eosin for immediate interpretation, or with Papanicolaou stain. The air-dried smears were stained with the Diff-Quik® stain. Cell block material was prepared from the needle rinses. The lesions were subsequently excised, and histological examination was performed.

Cytology Findings

The FNAB smears from the recurrent and metastatic ameloblastoma tumors were comparable, with some differences as described later. Both FNAB smears demonstrated basaloid small cells with round-to-oval nuclei, showing fine chromatin, smooth-to-clefted contours, single or multiple small...
nucleoli, some longitudinal grooves, and sometimes a tear-drop shape (Fig. 1). Cytoplasm was very scant-to-absent in the alcohol-fixed smears but appeared more abundant with tiny vacuoles and pale blue staining in the air-dried smears. The cells occurred singly and in dyshesive groups with nuclear molding and crowding (Figs. 1, 2). As well, a predominant architectural pattern was present in both smears. It consisted of fibrovascular stromal fragments with central cores of branching blood vessels merging into peripheral palisading basaloid tumor cells (Fig. 3). In the recurrent mandibular tumor, the palisading cells were more columnar with elongated nuclei with a delicate bluish purple material around blood vessels. In the metastatic ameloblastoma, some of the tissue fragments showed cystic cavities surrounded by tumor cells, with keratin material present in the background (Figs. 4–5). Both smears also showed rosette-like structures composed of palisading tumor cells arranged around fibrillary material (Fig. 1). Negative findings included the absence of nuclear pleomorphism, mitotic activity, tumor cell necrosis, metachromatic basement membrane material, dentin, and cementum.

Histology Findings
The cell block of the recurrent mandibular tumor showed fragments of bluish gray fibrovascular stroma with peripheral palisading basaloid cells (Fig. 6), as well as dyshesive
crowded groups of basaloid cells. The cell block of the metastatic ameloblastoma showed only scant small groups of basaloid cells.

The excised recurrent mandibular ameloblastoma showed a mixed pattern of follicular and plexiform areas. Some zones showed prominent fibrovascular stroma intermixed with islands of basaloid-to-columnar cells, similar to the cytological findings (Figs. 3, 7). The excised metastatic ameloblastoma to the lung and pleura showed a prominent plexiform pattern with focal follicular areas and evidence of squamous differentiation in the form of cystic cavities filled with keratin debris (Fig. 8), similar to the FNAB findings. Neither excised specimen showed necrosis, mitotic activity, or pleomorphism.

**Discussion**

Ameloblastoma is a rare tumor of odontogenic epithelium, which requires long-term follow-up due to its locally aggressive nature and propensity for multiple recurrences.²⁻⁴ The malignant (metastatic) ameloblastoma is identical histologically with ameloblastoma and is distinguished from the latter by demonstration of metastases.²⁻³ In contrast, the
Ameloblastic carcinoma shows morphological features of malignancy regardless of the presence of metastatic disease.\textsuperscript{3,13,14} The estimated incidence of malignant ameloblastoma is about 2\%, and there are fewer than 50 cases describing its histology in the English literature.\textsuperscript{2-7} The cytological features on FNAB of ameloblastoma are also underreported in the literature, with fewer than 20 cases of ameloblastoma,\textsuperscript{8-11} two cases of metastatic ameloblastoma,\textsuperscript{12,13} and two cases of ameloblastic carcinoma (one mixed with fibrosarcoma)\textsuperscript{15,16} reported previously. Levine and coworkers\textsuperscript{12} first described the cytological features of malignant ameloblastoma, which included round-to-oval primitive single cells with high nuclear-to-cytoplasmic ratios, which were comparable to our findings (Fig. 1). Small basaloid cells were typical findings in seven reported ameloblastomas and one metastatic ameloblastoma as well.\textsuperscript{8-10,13} Other characteristics of ameloblastoma (benign and malignant) on FNAB smears seem to depend on the histological variant. Specifically, prominent squamous differentiation as well as the basaloid cell population were noted in the smears of five acanthomatous variants of non-malignant ameloblastoma,\textsuperscript{8,9} which are similar to the findings of metastasis of ameloblastoma in our case (Figs. 5, 8). In a report of a plexiform and follicular variant of ameloblastoma,\textsuperscript{10} a combination of peripheral palisading columnar cells and central basaloid cells were identified, similar to our case. Fibrovascular stromal fragments with adherent tumor cells as identified in our case (Fig. 3) have not been previously reported in the FNAB of ameloblastoma or malignant ameloblastoma. However, they have been described in an FNAB of ameloblastic carcinoma.\textsuperscript{15}

The finding of basaloid primitive cells in FNAB smears from the jaw or lung raises numerous possibilities in the...
differential diagnosis. In the oral cavity and jaw regions, small-cell tumors which need to be considered include adenoid cystic carcinoma, undifferentiated squamous cell carcinoma, small cell carcinoma, melanoma, lymphoma, and other odontogenic tumors, especially the ameloblastic fibroma. The nuclear features (coarse chromatin, hyperchromatism) of small cell carcinoma appear overtly malignant compared to those of ameloblastoma. As well, the extensive necrosis and mitotic activity found in small cell carcinoma and the extracellular metachromatic basement membrane material in some adenoid cystic carcinomas are not identified in ameloblastomas. Lymphoma can be quickly discarded as a possibility when smears show cohesive cellular groups and fragments which lack the stippled or coarse chromatin of lymphoid cells. Similarly, melanoma cells show more dyshesion and more cytoplasm than ameloblastoma. Intranuclear pseudo-inclusions, cytoplasmic melanin, and macronucleoli, all absent in ameloblastomas, are also important clues to melanoma when present. In difficult cases, however, immunoperoxidase marker studies can help in the distinction. Melanoma cells co-express vimentin, S-100, and HMB-45, while ameloblastoma shows cytokeratin reactivity.4,13 Strict adherence to the cytologic criteria of malignancy as seen in squamous cell carcinoma, and the identification of a second basaloid cell population as seen in ameloblastoma aid in distinguishing these two entities.8 Finally, the absence of dentin or cementum in smears helps to exclude other odontogenic tumors. However, the amelo-
blastic fibroma can be similar cytologically to ameloblastoma, in that they both show small basaloid cells. It is the presence of a prominent second cell population composed of mesenchymal spindle cells which distinguishes ameloblastic fibroma as reported by Carillo and coworkers.\(^\text{17}\)

Similar differential diagnoses must be considered for small basaloid cell tumors of the lung, with the exception of non-metastasizing odontogenic tumors. Additional entities include the primitive tumors: Ewing’s sarcoma, primitive neuroectodermal tumor, and neuroblastoma as well as metastatic adamantinoma. Differentiation of the primitive tumors from ameloblastoma may be difficult. However, clues for ameloblastoma include squamous differentiation and palisading columnar cells. Distinction from adamantinoma can be more troublesome, especially if no history of a primary tumor is available. Typically, FNAB smears of adamantinoma are composed of spindle cells but may also show small round cells.\(^\text{18,19}\) No necrosis, pleomorphism, or squamous differentiation is seen, but mitotic activity can be frequent, in contrast to ameloblastoma.\(^\text{18}\)

The most frequent metastatic sites for ameloblastoma are lung, pleura, or hilar lymph nodes (75%), followed by cervical lymph nodes and spine (about 15%).\(^\text{2,3}\) In our case, metastatic disease was present in both lungs, with pleural invasion on one side. Usually, there is a history of multiple recurrences and surgical procedures prior to metastases, with a median disease-free interval after initial treatment of 9 years.\(^\text{2,3}\) However, our case was unusual in that metastatic disease was identified 35 years after excision of the primary without the typical history of recurrences and excisions. The median disease-free interval after initial treatment is reported as 9 years with a median survival time after metastasis of 2 years.\(^\text{2,3}\) Our case showed a disease-free interval of 35 years, with a survival time of 45 years after initial diagnosis and 10 years after metastatic disease.

The mechanism of metastatic spread is not known. Proposed theories include hematogenous and/or lymphatic spread, perhaps aided by repeated manipulation of the tumor, or direct aspiration of tumor cells into the respiratory tree.\(^\text{2,3,7}\)

In summary, FNAB of odontogenic tumors are frequently performed, and there is scant literature on the cytological findings of many of these tumors. In our case, FNAB was useful in identifying both recurrent and metastatic ameloblastoma, allowing definitive treatment for the patient. The cytological features of ameloblastoma seem to be characteristic. However, they may not be recognized by the unwary observer, especially at metastatic sites, due to the few reported cases in the literature.

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References